

Claims:

1. A pharmaceutical composition for the treatment of the risk factors of syndrome X of Reaven comprising as active ingredient a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.
2. A pharmaceutical composition comprising an additional compound.
3. A pharmaceutical composition comprising an additional compound having an additional pharmaceutical effect.
4. A pharmaceutical composition according to Claim 2 or 3 wherein the additional compound is selected among carriers, solvents and emulgators.
5. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Octreotide.
6. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Vapreotide.
7. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog of somatostatin is Lanreotide.
8. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs of somatostatin are Cyclopeptide somatostatin analogues selected among :
- Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
 Cyclo[N-Me-Ala-Tyr-D-Trp-Lys-Val-Phe]
 Cyclo[Pro-Ala-D-Trp-Lys-Thr-Phe]
 Cyclo[Pro-Tyr-D-Trp-Lys-Thr-Phe]
 Cyclo[Pro-Phe-D-Trp-Lys- δ -aminobutyric-Phe]
 Cyclo[N-Me-Ala-Phe-D-Trp-Lys-Thr-Phe]
 Cyclo[Pro-Phe-D-Trp-Lys-Val-Phe]
 Cyclo[D-Ala-D-Phe-D-Trp-L-Lys-D-Thr-N-Me-D-Phe]
 Cyclo[Pro-Phe-D-Trp-Lys-Thr(Bzl)] (Bzl = (a))
 Cyclo[Pro-Phe-D-Trp-Lys-Thr-Phe]
 Cyclo[Pro-D-Phe-D-Trp-Lys-Thr(Bzl)]
 Cyclo[Ahep-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Tyr-Thr-Ser] (Ahep = (b))
 Cyclo[Ahep-Phe-D-Trp-Lys-Thr(Bzl)]
 Cyclo[Ahep-Phe-D-Trp-Lys-Thr]

09254600-03199

Cyclo[Ahep-Phe-D-Trp-Lys-Ser(Bzl)]

Cyclo[Ahex-Phe-D-Trp-Lys-Thr(Bzl)]

(Ahex = (c))

Cyclo[Aoct-Phe-D-Trp-Lys-Thr(Bzl)]

(Aoct = (d))

Cyclo[Ala-Cys-Phe-D-Trp-Lys-Thr-Cys]

(a) Bzl = benzyl

(b) Ahep = 7-aminoheptanoyl

(c) Ahex = 6-aminohexanoyl

(d) Aoct = 8-amino-octanoyl;

Claim 1

9. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Phe-[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol

Claim 1

10. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH₂

(Nal = (1))

Claim 1

11. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Phe-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH₂

Claim 1

12. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Phe-[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH₂

Claim 1

13. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Phe-[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Nal-NH₂

(Abu = (2))

Claim 1

14. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Phe-[Cys-Tyr-D-Trp-Lys-Ser-Cys]-Nal-NH₂

Claim 1

15. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Nal-[Cys-Tyr-D-Trp-Lys-Val-Cys]-Nal-NH₂

Claim 1

16. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

c(Ahep-Trp-D-Trp-Lys-Thr-Phe)

Claim 1

17. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Phe-Cpa-Tyr-D-Trp-Lys-Thr-Phe-Thr-NH₂

(Cpa = (4))

Claim 1

18. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analog is:

D-Phe-Cpa-Tyr-D-Trp-Lys-Val-Phe-Thr-NH₂

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19. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂ *Claim 1*
20. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂ *Claim 1*
21. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂ *Claim 1*
22. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analog is:
D-Phe-Ala-Phe-D-Trp-Lys-Ala-Nal-NH₂ *Claim 1*
23. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Val-Phe-Thr-NH₂ *Claim 1*
24. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analog is:
D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH₂ *Claim 1*
25. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analog is:
D-Phe-Phe-Tyr-D-Trp-Lys-Val-Phe-D-Nal-NH₂ *Claim 1*
26. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analogs are polypeptides of the formula:
X-Lys-Asn-Phe-Phe-A-Lys-Thr-Phe-Thr-Ser-Y
wherein A is L- or D-Trp,
X is H-(Aeg)_m-Cys- or H-(Aeg)_m-Ala-Gly-Cys-,
Y is -Cys-(Aeg)_n-OH or
X and Y taken together are a 2-aminoethyl-glycyl group in the ring position and
m and n are 0, 1, 2, provided that
m and n are at least 1,
and their cyclic disulfide derivatives. *Claim 1*
27. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analogs are peptides of the formula:

Bmp-Lys-X-Phe-Phe-trp-Lys-Thr-Phe-Thr-Y-Cys-OH
 3 4 5 6 7 8 9 10 11 12 13 14

in which

Bmp represents the desaminocysteine radical,
 X represents Asn,
 trp represents D-Trp that may be substituted
 in the benzene ring by a halogen atom, and
 Y represents the radical of an alpha-(lower
 alkyl)amino-(lower alkyl)-carboxylic acid
 having a minimum of 4 and a maximum of 8
 carbon atoms, in which the two lower alkyl
 radicals can be connected to one another with
 a single C-C bond, an oxygen atom or a sulphur (II)
 atom.

28. A pharmaceutical composition according to ^{Claim 1} ~~any of Claims 1 to~~
 4, wherein the somatostatin analogs are cyclic octapeptides
 of the formula

Asn-Phe-Phe-Trp-Lys-Thr-Phe-Gaba(Ar)
 5 6 7 8 9 10 11 12

in which

Trp represents L-Trp or D-Trp, in which the
 benzene ring may be substituted by a
 fluorine atom, and
 Gaba(Ar) represents the residue of α -aminobutyric
 acid substituted by a cyclic hydrocarbonyl
 radical Ar selected from the group consisting
 of cyclohexyl; phenyl optionally substituted
 by halogen, nitro or phenoxy; and naphthyl
 optionally substituted by halogen.

29. A pharmaceutical composition according to ^{Claim 1} ~~any of Claims 1 to~~
 4, wherein the somatostatin analogs are compounds of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-R₈
 -Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-R₁₈-R₁₉-Phe-Phe-D
 -Trp-Lys-Thr-R₂₅-R₂₆-R₂₇-R₂₈-OH wherein R₈ is

Met or Leu, R_{18} is Lys or des R_{18} , R_{19} is Asn or

des R_{19} , R_{25} is Phe or Tyr, R_{26} is Thr or des

R_{26} , R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys.

CLAIM 1

Q 30.

A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analogs are compounds of formula

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala- R_8 -Ala-Pro

-Arg-Glu-Arg-Lys-Ala-Gly-Cys- R_{18} - R_{19} -Phe-Phe-D-Trp-Lys

-Thr- R_{25} - R_{26} - R_{27} - R_{28} -OH wherein R_8 is Met or

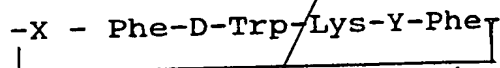
Leu, R_{18} is Lys or des R_{18} , R_{19} is Asn or des

R_{19} , R_{25} is Phe or Tyr, R_{26} is Thr or des R_{26} ,

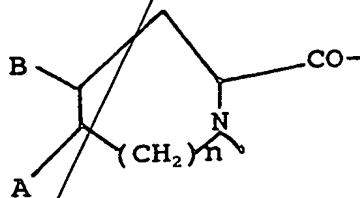
R_{27} is Ser or D-Ser and R_{28} is D-Cys or Cys, or the linear version thereof where the disulfide bridge is replaced by hydrogen.

Q 31.

A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analogs are cyclic hexapeptides of the formula



in which X represents the radical of an L-aminoacid of the formula



in which A and B are identical or different and denote alkyl having 1 to 3 carbon atoms, or A and B together represent a saturated, unsaturated or aromatic monocyclic or bicyclic structure having 3 to 6 carbon atoms,

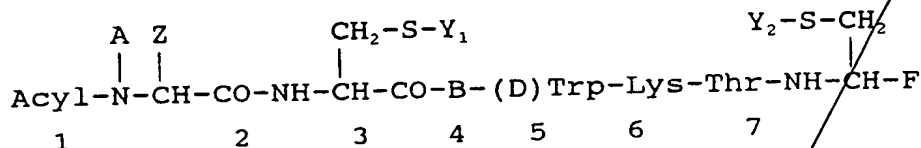
n denotes 0 or 1, and

Y represents an aliphatic or aromatic L-aminoacid the side-

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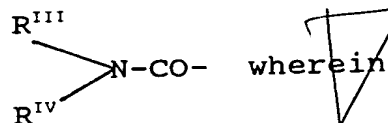
chair of which can be hydroxylated, said amino acid being selected from the group consisting of L-alanine, L-serine, L-valine, L-leucine, L-isoleucine, L-phenylalanine and L-tyrosine.

32. A pharmaceutical composition according to any of claims 1 to 4, wherein the somatostatin analogs are N-acyl-polypeptides of formula,



wherein

"Acyl" is a group of formula $\text{R}^{\text{I}}\text{CO-}$ wherein R^{I} is C_{1-20} alkyl or phenyl; a group of formula $\text{R}^{\text{II}}\text{SO}_2\text{-}$ wherein R^{II} is C_{1-20} alkyl, phenyl or tolyl; a group



R^{III} and R^{IV} are each independently hydrogen or C_{1-10} alkyl; or biotinyl,

A is hydrogen or C_{1-3} alkyl,

$>\text{N-CH(Z)-CO-}$ is an (L)- or (D)-phenylalanine residue optionally ring-substituted by NO_2 , or an (L) or (D)-norleu-

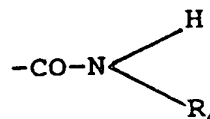
cine residue,

whereby

Z in $>\text{N-CH(Z)-CO-}$ represents the remainder of said residue,

B is -Phe- optionally ring-substituted by NO_2 ,

F is a group of formula

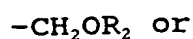


wherein R_4 is hydrogen or a group of formula

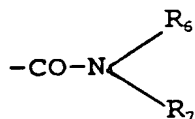


R_5 is $\text{CH}_3\text{CH(OH)-}$, i-butyl or benzyl

X is a group of formula -COOR_1 ,



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wherein R₁, R₅ and R₇ are each hydrogen or C₁₋₃alkyl, and

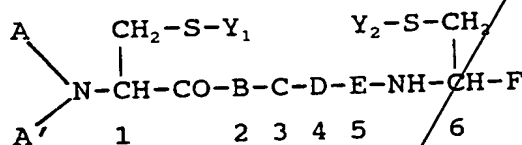
R₂ is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

the group $-\text{CH}(\text{R}_5)-\text{X}$ having the (D)- or (L)-configuration, and

Y_1 and Y_2 are each hydrogen or together represent a direct bond, whereby the residue resides in the 2- and 7-position each independently have the (L)- or (D)-configuration, and with the proviso that:

i) (L)- and/or (D)-cysteine residues are present at the 2- and 7-positions only. Claim 1

33. A pharmaceutical composition according to ~~any of claims 1 to 4~~, wherein the somatostatin analogs are polypeptides of the formula



wherein

wherein
A is C₁₋₁₂alkyl, C₇₋₁₀phenylalkyl or a group of formula RCO-,
whereby

i) R is hydrogen, C₁₋₁₁alkyl, phenyl or C₇₋₁₀phenylalkyl, or

ii) RCO- is a) an L- or D-phenylalanine residue optionally ring-substituted by halogen and/or C₁₋₃alkyl,
b) H-Asn-, or
c) H-Nle-Asn-,

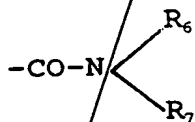
the α -amino group of amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di-C₁₋₁₂alkylated,

- A' is hydrogen or, when A is C₁₋₁₂alkyl or C₇₋₁₀phenylalkyl, also C₁₋₁₂alkyl or C₇₋₁₀phenylalkyl,
 B is -Phe- optionally ring-substituted by halogen and/or C₁₋₃alkyl,
 C is -(L)- or -(D)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen and/or C₁₋₃alkyl,
 D is -Lys- optionally α -N-methylated and optionally Σ -N-C₁₋₃-alkylated,
 E is -Thr- or -Ala- each in (D)- or (L)-form and each being optionally α -N-methylated,

F is a group of formula $-\text{COOR}_1$, $-\text{CH}_2\text{OR}_2$, $-\text{CO}-\text{N} \begin{array}{l} \nearrow \text{R}_3 \\ \searrow \text{R}_4 \end{array}$ or



- wherein R₁ is hydrogen or C₁₋₃alkyl,
 R₂ is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R₃ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀phenylalkyl,
 R₄ is hydrogen, C₁₋₃alkyl or, when R₃ is hydrogen or methyl, also a group of formula $-\text{CH}(\text{R}_5)-\text{X}$,
 R₅ is hydrogen, $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, $-\text{CH}_2-\text{OH}$, $-\text{CH}(\text{CH}_3)-\text{OH}$, isobutyl or benzyl
 X is a group of formula $-\text{COOR}_1$, $-\text{CH}_2\text{OR}_2$ or

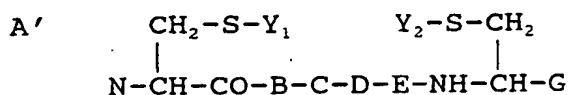


wherein

- R₁ and R₂ have the meanings given above,
 R₆ is hydrogen or C₁₋₃alkyl and
 R₇ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀phenylalkyl,

the group $-\text{CH}(\text{R}_5)-\text{X}$ having the D- or L- configuration, and Y_1 and Y_2 are each hydrogen or together represent a direct bond, whereby the residues in the 1- and 6-position each independently have the L- or D-configuration.

34. A pharmaceutical composition according to ~~any of Claims 1 to 4~~, wherein the somatostatin analog is a compound of formula



A

wherein

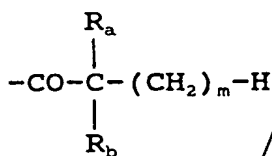
A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula $\text{RCO}-$, whereby

- i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl or
- ii) $\text{RCO}-$ is
 - a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy;
 - b) the residue of a natural or synthetic α -amino acid other than defined under a) above or of a corresponding D-amino acid, or
 - c) a dipeptide residue in which the individual amino acid residues are the same or different and are selected from those defined under a) and/or b) above,

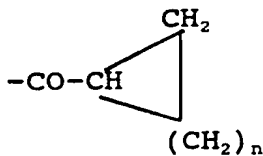
C_{1-8} alkanoyl,

A' is hydrogen,

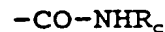
Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of formulae (1) to (5).



(1)

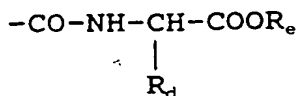


(2)

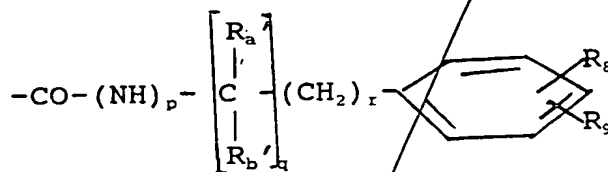


(3)

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(4)

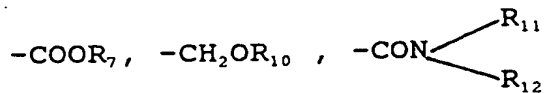


(5)

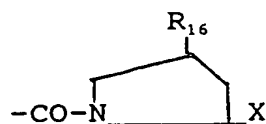
wherein

- R_a is methyl or ethyl
 R_b is hydrogen, methyl or ethyl
 m is a whole number from 1 to 4
 n is a whole number from 1 to 5
 R_c is (C_{1-6}) alkyl
 R_d represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen)
 R_e is (C_{1-5}) alkyl
 R_a' and R_b' are independently hydrogen, methyl or ethyl,
 R_8 and R_9 are independently hydrogen, halogen, (C_{1-3}) alkyl or (C_{1-3}) alkoxy,
 p is 0 or 1,
 q is 0 or 1, and
 r is 0, 1 or 2,
 B is -Phe- optionally ring-substituted by halogen, NO_2 , NH_2 , OH , C_{1-3} alkyl and/or C_{1-3} alkoxy (including pentafluoroalanine), or β -naphthyl-Ala
 C is (L)-Trp- or (d)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen, NO_2 , NH_2 , OH , C_{1-3} alkyl and/or C_{1-3} alkoxy,
 D is Lys, Lys in which the side chain contains 0 or S in β -position, F-Lys or δ F-Lys, optionally α -N-methylated, or a 4-aminocyclohexylAla or 4-aminocyclohexylGly residue
 E is The, Ser, Val, Phe, Ile or an aminoisobutyric or aminobutyric acid residue
 G is a group of formula

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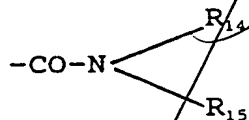


or



wherein

- R_7 is hydrogen or C_{1-3} alkyl,
 R_{10} is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,
 R_{11} is hydrogen, C_{1-9} alkyl, phenyl or C_{7-10} phenyl-alkyl,
 R_{12} is hydrogen, C_{1-3} alkyl or a group of formula $-\text{CH}(\text{R}_{13})-\text{X}_1$,
 R_{13} is CH_2OH , $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, or $-\text{CH}(\text{CH}_3)\text{OH}$ or represents the substituent attached to the α -carbon atom of a natural or synthetic α -amino acid (including hydrogen) and
 X_1 is a group of formula $-\text{COOR}_7$, $-\text{CH}_2\text{OR}_{10}$ or



wherein

- R_7 and R_{10} have the meanings given above,
 R_{14} is hydrogen or C_{1-3} alkyl and
 R_{15} is hydrogen, C_{1-3} alkyl, phenyl or C_{7-10} phenylalkyl, and
 R_{16} is hydrogen or hydroxy,

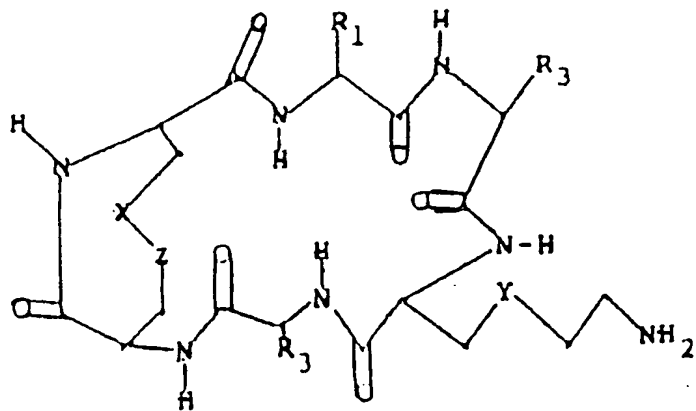
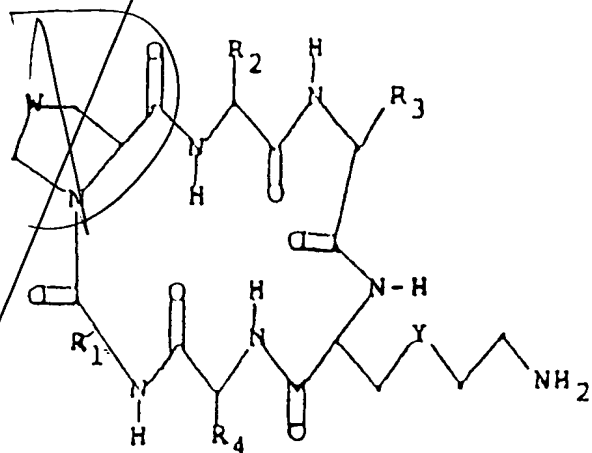
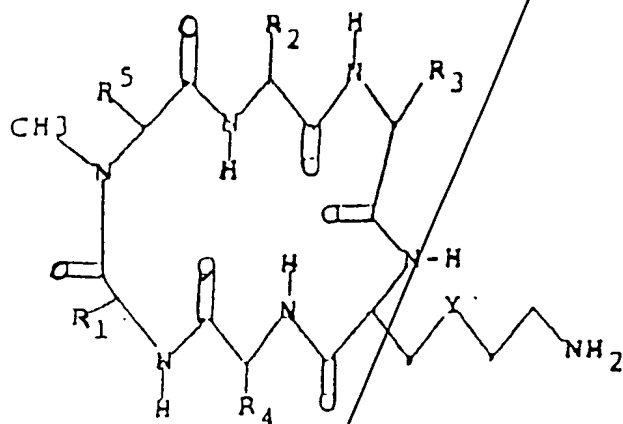
with the proviso that

when R_{12} is $-\text{CH}(\text{R}_{13})-\text{X}_1$ then R_{11} is hydrogen or methyl,

wherein the residues B, D and E have the L-configuration, and the residues in the 2-and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)- configuration.

35. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analog is a somatostatin analog selected from the compounds of the following formulae

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wherein

W is

one of X and Z

Y is

each of R_1 and R_2

S or $(CH_2)_s$ where s is 0, 1 or 2;

is S and the other is S or CH_2 ;

S or $(CH_2)_t$ where t is 0, 1 or 2;

independently of the other, is C_{1-5} alkyl, benzyl, benzyl having one or two C_{1-5} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-5} alkoxy substituents, or C_{1-5} alkyl substituted with 5- or 6-membered heterocyclic ring;

R_3 is

3-indolymethyl, either unsubstituted or having C_{1-5} alkyl, C_{1-5} alkoxy or halogen substitution;

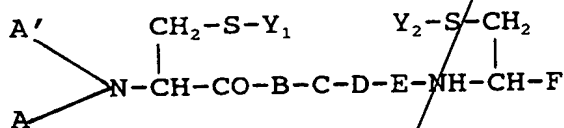
R_4

C_{1-5} alkyl, C_{1-5} hydroxyalkyl, benzyl, carboxy- $(C_{1-5}$ alkyl), amino (C_{1-5} alkyl) or benzyl having a C_{1-5} alkyl, halogen, hydroxy, amino, nitro and/or C_{1-5} alkoxy substituent;

R_5 is

C_{1-5} alkyl, benzyl, or benzyl having a C_{1-5} alkyl, halogen, hydroxy, amino, nitro, and/or C_{1-5} alkoxy substituent,

compounds of formula



wherein

A is C_{1-12} alkyl, C_{7-10} phenylalkyl or a group of formula $RCO-$, whereby

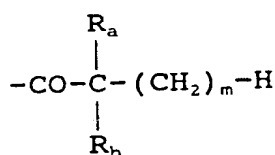
- i) R is hydrogen, C_{1-11} alkyl, phenyl or C_{7-10} phenylalkyl, or
- ii) $RCO-$ is
 - a) an L- or D-phenylalanine residue optionally ring-substituted by F, Cl, Br, NO_2 , NH_2 , OH, C_{1-3} alkyl and/or C_{1-3} alkoxy
 - b) the residue of a natural α -amino acid other than defined under a) above or of a corresponding D-amino acid, or
 - c) a dipeptide residue in which the individual amino acid

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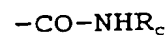
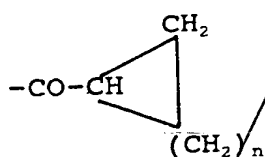
residues are the same or different and are selected from those defined under a) and/or b) above, the α -amino group or amino acid residues a) and b) and the N-terminal amino group of dipeptide residues c) being optionally mono- or di- C_{1-12} alkylated,

A' is hydrogen or, when A is C_{1-12} alkyl or C_{7-10} phenylalk- also C_{1-12} alkyl or C_{7-10} phenylalkyl,

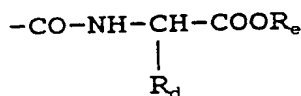
Y_1 and Y_2 represent together a direct bond or each of Y_1 and Y_2 is independently hydrogen or a radical of the formulae



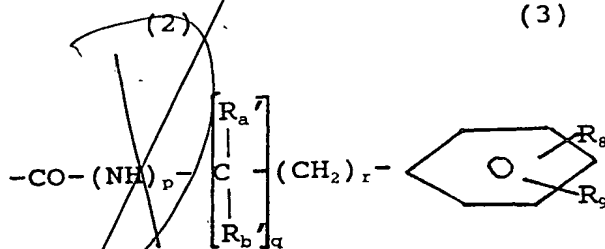
(1)



(3)



(4)



(5)

wherein R_a is methyl or ethyl

R_b is hydrogen, methyl or ethyl

m is a whole number from 1 to 4

n is a whole number from 1 to 5

R_c is (C_{1-6}) alkyl

R_d represents the substituent attached to the α -carbon atom of a natural α -amino acid (including hydrogen)

R_e is (C_{1-5}) alkyl

R_a' and R_b' are independently hydrogen, methyl or ethyl,

R_8 and R_9 are independently hydrogen, halogen, (C_{1-3}) alkyl or (C_{1-3}) alkoxy,

p is 0 or 1,

q is 0 or 1, and

r is 0, 1 or 2,

B is -Phe- optionally ring-substituted by halogen, NO_2 , NH_2 ,

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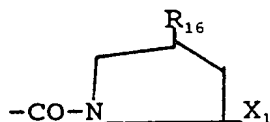
OH, C₁₋₃alkyl and/or C₁₋₃alkoxy, or naphthylalanine.

C is (L)-Trp- or (D)-Trp- optionally α -N-methylated and optionally benzene-ring-substituted by halogen, NO₂, NH₂, OH, C₁₋₃ alkyl and/or C₁₋₃ alkoxy,

D is -Lys-, ThiaLys, F-Lys, δ F-Lys or Orn, optionally α -N-methylated, or a 4-aminocyclohexyl Ala or 4-aminocyclohexyl Gly residue,

E is Thr, Ser, Val, Phe, Ile or an aminoisobutyric acid residue

F is a group of formula $-\text{COOR}_7$, $-\text{CH}_2\text{OR}_{10}$, $-\text{CON} \begin{matrix} \nearrow \text{R}_{11} \\ \searrow \text{R}_{12} \end{matrix}$ or



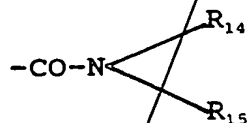
wherein R₇ is hydrogen or C₁₋₃alkyl,

R₁₀ is hydrogen or the residue of a physiologically acceptable, physiologically hydrolysable ester,

R₁₁ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀-phenylalkyl,

R₁₂ is hydrogen, C₁₋₃alkyl or a group of formula $-\text{CH}(\text{R}_{13})-\text{X}_1$,

R₁₃ is CH₂OH, $-(\text{CH}_2)_2-\text{OH}$, $-(\text{CH}_2)_3-\text{OH}$, or $-\text{CH}(\text{CH}_3)\text{OH}$ or represents the substituent attached to the α -carbon atom of a natural α -amino acid (including hydrogen) and X₁ is a group of formula $-\text{COOR}_7$, $-\text{CH}_2\text{OR}_{10}$ or



wherein

R₇ and R₁₀ have the meanings given above,

R₁₄ is hydrogen or C₁₋₃alkyl and

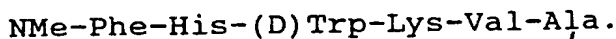
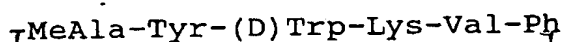
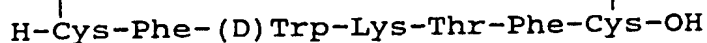
R₁₅ is hydrogen, C₁₋₃alkyl, phenyl or C₇₋₁₀phenylalkyl, and

R₁₆ is hydrogen or hydroxy,

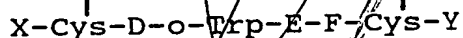
with the proviso that

when R₁₂ is $-\text{CH}(\text{R}_{13})-\text{X}_1$ then R₁₁ is hydrogen or methyl,

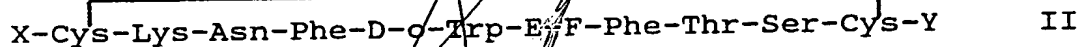
wherein the residues B, D and E have the L-configuration, and the residues in the 2- and 7-position and any residues Y_1 4) and Y_2 4) each independently have the (L)- or (D)-configuration and compounds of the following formulae



36. A pharmaceutical composition according to any of Claims 1 to 4, wherein the analogs are Somatostatin analogs



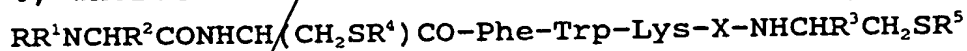
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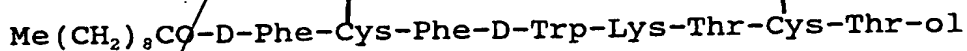
II

I, II, X = N-terminus anchor; Y = C-terminus anchor, G-I or its alc; wherein at least I of X, Y = cationic anchor; D = Phe Tyr, 3-(p-fluorophenyl)alanine or 3 (p-chlorophenyl)alanine residue; E = Lys, Lys(R^1); R^1 = C_{1-8} (fluoro)alkyl; F = Thr, Val, Ser; G = D- or L-Thr, Phe, or 3-(2-naphthyl)alanine residue; I = OH, NH_2 , NHR^1 .

37. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analogs are peptides:



[R = inorg. or org. acyl group, R^1 = H, alkyl, $NCHR^2\text{CO}$ moiety = I.



I

or D-Phe (optionally ring substituted by halo, NO_2 , OH, alkyl, alkoxy); Phe, Trp, (D or L), may be ring substituted by NO_2 , NH_2 , OH, alkyl, alkoxy; Lys may be α -N-methylated and Σ -N-alkylated; X = D- or L- α -amino acid residue optionally α -N-methylated; R^3 = CO_2H , CH_2OH , carbamoyl, R^4 = R^5 = H, R^4R^5

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= bond]

38. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-X-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly

Cys-X¹-X²-Phe-Phe-D-Trp-Lys-Tys-Thr-X³-X⁴-X⁵-X⁶-OH

39. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Leu-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-

Cys-Lys-Asn-Phe-Phe-D-Trp-Lys-Thr-Tyr-Thr-Ser-Cys-OH

40. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is

c(Spacer-Phe-D-Trp-Lys-Thr)

Spacer may stand for:

- a) R,S- δ -Bn-o-AMPA
- b) R- α -Bn-NMe-o-AMPA
- c) Phe-Pro

41. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H₂N-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

42. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

H₂N-Ser-Ala-Asn-Ser-Asn-Pro-Ala-Met-Ala-Pro-Arg-Glu-Arg-Lys-Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys-OH

43. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

D- β -Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂

44. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

Ac-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂

45. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:

D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Trp-NH₂

46. A pharmaceutical composition according to any of Claims 1 to

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- 4, wherein the somatostatin analog is:
D-Trp-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-NH₂
47. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂
48. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
D-Phe-Cys-Tyr-D-Trp-Lys-Val-Cys-Trp-NH₂
49. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
3-(2-naphthyl)-D-Ala-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂
50. A pharmaceutical composition according to any of Claims 1 to 4, wherein the somatostatin analog is:
c(Aha-Phe-p-Cl-Phe-D-Trp-Lys-Thr-Phe)
Aha = 7 -amino heptanoic acid.
51. A pharmaceutical composition according to any of Claims 1 to 4, wherein the active ingredient is diazoxide and comprises in addition a thiazide selected among chlorothiazide, hydrochlorothiazide, trichloromethiazide and polythiazide.
52. A method for the treatment of symptoms of syndrome X by applying to a patient a pharmaceutical composition according to any of Claims 1 to 51 comprising a pharmaceutically effective dosage of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin.
53. A method according to Claim 52, wherein the pharmaceutically effective dosage (calculated on octreotide) does not exceed 50 µ/kg/day.
54. A method according to Claim 53, wherein said dosage does not exceed 40 µ/kg/day.
55. A method according to any of Claims 52 to 54 wherein the analog is Octreotide which is applied in the form of an injection in a 0.9% saline solution.
56. A method according to Claim 52, wherein said dosage does not exceed 8 mg/kg/day in the treatment of the active ingredient (calculated on diazoxide) in adults, and does not exceed 15/mg/day in the treatment of children.

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57. A method according to Claim 52, wherein the amount of metformin applied does not exceed 2.5 g/day divided into 2 - 3 portions.
58. Use of a compound selected among somatostatin or one of its analogs (as herein defined), diazoxide or one of its analogs (as herein defined), cyclothiazide or one of its analogs (as herein defined) and metformin in a preparation for the treatment of the risk factors of syndrome X of Reaven substantially as described in the specification.

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ADD
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